



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-1276]

Meta-Analyses of Randomized Controlled Clinical Trials (RCTs) for the Evaluation of Risk to Support Regulatory Decisions; Notice of Public Meeting; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public meeting; request for comments.

The Food and Drug Administration (FDA or the Agency) is announcing a public meeting to obtain input on scientific approaches for the conduct and assessment of meta-analyses of randomized controlled clinical trials (RCTs) to evaluate safety risks associated with the use of human drugs or biological products within the framework of regulatory decisionmaking. The term meta-analysis refers to the combining of evidence from independent studies using appropriate statistical methods. The purpose of the public workshop is to initiate constructive discussion and information sharing among regulators, researchers, health care providers, representatives from the pharmaceutical industry and health care organizations, and others from the general public, about the use of meta-analyses of randomized trials as a tool for safety assessment in the regulation of pharmaceutical products. The format of the meeting consists of a series of presentations describing and illustrating the methodological issues that arise in the use of meta-analyses to evaluate safety risks, followed by a discussion of those issues from invited panelists and audience members. This meeting satisfies an FDA commitment that is part of the fifth authorization of the Prescription Drug User Fee Act (PDUFA V). The input from the

meeting will be used to develop a draft guidance that describes best practices for the conduct of meta-analyses and FDA's intended approach for the use of meta-analyses in regulatory decision-making. FDA is also publishing a white paper to facilitate discussion at the public meeting, which is available online at

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm360080.htm>. The public is invited to comment on this paper through Docket Number FDA-2013-N-1276 and at the public meeting.

Date and Time: The meeting will be held on November 25, 2013, from 8:30 a.m. to 4:30 p.m.

Location: The public meeting will be held at FDA's White Oak Campus, 10903 New Hampshire Ave., Bldg. 31, rm. 1503, Silver Spring, MD 20993. Entrance for public meeting attendees is through Building 1, where routine security check procedures will be performed. For parking and security information, please refer to

<http://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241740.htm>.

Contact: Indira Hills, Food and Drug Administration, Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Bldg. 21, rm. 4508, Silver Spring, MD 20993, 301-796-9686, FAX: 301-796-9907, email: indira.hills@fda.hhs.gov.

Registration and Requests for Oral Presentation: The FDA Conference Center at the White Oak location is a Federal facility with security procedures and limited seating. Individuals who wish to attend the public meeting must register on or before November 18, 2013, by visiting <https://www.surveymonkey.com/s/QRKMGNY> and contacting Indira Hills (see Contact Person). Early registration is recommended. Registration is free and will be on a first-come, first-served

basis. However, FDA may limit the number of participants from each organization based on space limitations. Onsite registration on the day of the meeting will be based on space availability.

Time will be reserved during the meeting for planned presentations from the audience. If you would like to present at the meeting, please indicate this in your meeting registration. Time for audience presentations is limited and will be assigned on a first-come, first-served basis. Note also that time will be designated throughout the day for general comments and questions from the audience following the panel discussions.

In this Federal Register notice, FDA has included specific issues that will be addressed by the panel. If you wish to address one or more of these issues in your presentation, please indicate this at the time you register so that FDA can consider that in organizing the presentations. FDA will do its best to accommodate requests to speak, and will determine the amount of time allotted to each presenter and the approximate time that each oral presentation is scheduled to begin. An agenda will be available approximately 2 weeks before the meeting at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm360080.htm>.

If you need special accommodations because of disability, please contact Indira Hills (see Contact Person) at least 7 days before the meeting.

Streaming Webcast of the Public Meeting: A live webcast of this meeting will be viewable at <https://collaboration.fda.gov/metaanalysis1113/> on the day of the meeting. A video record of the meeting will be available at the same web address for 1 year.

Comments: Regardless of attendance at the public meeting, interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or

written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. To ensure consideration, submit comments by December 16, 2013. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Transcripts: Please be advised that as soon as a transcript is available, it will be accessible at <http://www.regulations.gov>. It may be viewed at the Division of Dockets Management (see Comments). A transcript will also be available in either hard copy or on CD-ROM, after submission of a Freedom of Information request. Written requests are to be sent to the Division of Freedom of Information (ELEM-1029), Food and Drug Administration, 12420 Parklawn Dr, Element Bldg., Rockville, MD 20857.

SUPPLEMENTARY INFORMATION:

I. Background

On July 9, 2012, the President signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144). Title I of FDASIA reauthorizes PDUFA and provides FDA with the user fee resources necessary to maintain an efficient review process for human drug and biological products. The reauthorization of PDUFA includes performance goals and procedures for the Agency that represent FDA's commitments during fiscal years 2013-2017. These commitments are fully described in the document entitled "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017" ("PDUFA Goals Letter"), available on FDA's Web site at

<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>

f. Section IX of the PDUFA Goals Letter, titled “Enhancing Regulatory Science and Expediting Drug Development,” includes an enhancement to advance the science of meta-analysis methodologies. As part of this enhancement, FDA committed to hold a public meeting to engage stakeholders in a discussion of current and emerging scientific approaches and methods for the conduct of meta-analyses and to facilitate stakeholder input regarding the use of meta-analyses in FDA’s regulatory review process. The public meeting announced by this notice will fulfill this commitment.

II. Purpose and Scope of the Meeting

The objectives of the meeting are to:

1. Initiate constructive discussion and information-sharing about best practices in meta-analyses of clinical trial data that can be used to evaluate potential drug risks while limiting spurious findings,
2. Share current experience regarding the criteria considered by FDA to be important in making regulatory decisions when evaluating the strength and quality of evidence provided by a meta-analysis, and
3. Obtain input on specific issues identified by FDA on procedures, methods, and potential sources of bias in the design, conduct and use of meta-analysis.

Although many external stakeholders conduct meta-analyses, FDA’s use of meta-analyses and other safety evaluation tools has the potential to result in consequential regulatory actions, including market withdrawal or concluding that a safety concern is not supported by data. As a result, FDA must adopt a rigorous approach to these analyses and be transparent regarding its evidentiary standards and how it weighs the evidence of a meta-analysis in arriving

at a decision or regulatory action. The public meeting will focus on meta-analyses conducted for purposes of safety evaluation using data from RCTs.

FDA acknowledges that meta-analyses conducted to evaluate a product's effectiveness, either overall or within specific subgroups, are occasionally of interest to the Agency, but the primary use of meta-analyses in the regulatory setting is for the assessment of product risk. Furthermore, although meta-analyses of non-randomized studies may be informative for the assessment of certain safety endpoints, the issues related to such a meta-analysis are not the focus of the meeting.

FDA expects that this meeting will build upon prior stakeholder feedback on the design, conduct, and assessment of meta-analyses obtained at the "DIA/FDA Best Practices for Regulatory Information Synthesis of Randomized Controlled Trials for Product Safety Evaluation" workshop held on March 10 and 11, 2011, in Bethesda, MD.

The public input from the meeting will be used to develop a draft guidance describing best practices for the conduct and use of meta-analyses of randomized controlled trials for the evaluation of risks associated with the use of human drugs or biological products within the framework of regulatory decisionmaking. The future guidance will be intended for FDA reviewers, the pharmaceutical industry, and for third-party entities that prepare or evaluate meta-analyses to assess the safety of regulated products, as there is currently no FDA guidance in this area. Specifically, this guidance will describe FDA's view of various aspects of the criteria considered important when evaluating the strength and quality of evidence provided by a meta-analysis.

To facilitate discussions at the public meeting, FDA is publishing a white paper on considerations in the conduct and use of meta-analyses of RCTs that are intended to support regulatory decisionmaking about a product's safety. This document is available on FDA's Web site at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm360080.htm>.

III. Scope of Public Input Requested

FDA seeks input on a range of topics related to the design and conduct of meta-analyses and the interpretation of meta-analysis results when evaluating risk in the regulation of pharmaceutical products. These include the following:

1. Potential sources of bias that may arise in designing a meta-analysis, including:
 - a. Advance or prior knowledge of individual study results and their influence on study selection.
 - b. Lack of or inadequate pre-specification of the meta-analysis hypothesis.
 - c. Inclusion of the hypothesis-generating study in the meta-analysis designed to confirm the hypothesis.
 - d. Other sources of bias that may exist but cannot be identified.
2. Potential for spurious findings because of the examination of multiple hypotheses, endpoints, and subgroups, and use of data driven analyses, in a meta-analysis.
3. Methodological issues in the conduct of the meta-analysis, including the following:
 - a. The use of fixed versus random effects models in evaluating a meta-analytic hypothesis, especially with regard to individual and overall study power, study heterogeneity, and generalizability.

- b. The relative value of the use of frequentist versus Bayesian methods for meta-analyses.
 - c. The choice of statistical levels of uncertainty of the results, including the significance level for the primary and secondary hypotheses.
 - d. The most appropriate methods to incorporate studies with few events and those with no events.
4. Issues related to the individual studies constituting a meta-analysis, including:
- a. Measures of individual study quality, including availability of protocols and amendments.
 - b. Outcome and exposure ascertainment in each study.
 - c. The use of patient-level versus study-level data.
5. Issues related to the overall quality of the meta-analysis, including the following:
- a. Whether there is adequate documentation of the pre-specification and proper conduct of a meta-analysis, and more generally, how researchers should document their methods, including the important issues of pre-specification, in support of their proper conduct of a meta-analysis.
 - b. Use and pre-specification of the types of sensitivity analyses to evaluate the impact of various sources of bias (see section III.1) on the meta-analysis findings.
 - c. Evaluating the results of a meta-analysis when one or a few large studies dominate the findings (often recognized before the analysis).
 - d. The overall framework to evaluate the quality of the meta-analysis; whether there is a basis for establishing a hierarchy of evidence for judging the quality of the meta-analysis.

Dated: October 21, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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